

# Complex Times for Earthquakes, Stocks, and the Brain's Activity

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A new study by He et al. in this issue of *Neuron* shows that large-scale arrhythmic (1/f) brain activity contains nested temporal structure in the form of crossfrequency coupling. This suggests temporal organization in neural mass activity beyond oscillations and draws attention to ubiquitous but often ignored arrhythmic patterns in neural activity.

What do earthquakes, Dow-Jones, and brain activity have in common? Unpredictability first springs to mind, of course, but as researchers have long noticed, these and many other complex processes might actually share common patterns pertaining to long-range spatio-temporal correlations of the underlying quantities (Kello et al., 2010; Jensen, 1998). In addition, and as an intriguing study in this issue of *Neuron* illustrates (He et al., 2010), they might also share another level of temporal organization, whereby the phase of slower timescales predicts the amplitude of faster ones. This nesting of timescales might open a window onto the complex structure of neural activity, but also raises questions with regard to its universality.

In their new study, He et al. recorded electrocorticographic (ECoG) activity across several brain areas in human patients. To investigate the signal's temporal structure, they calculated the frequency spectrum, i.e., the distribution of amplitudes of individual frequency bands as a function of frequency. In concordance with previous studies, they described the frequency spectra using the power-law  $1/f^a$ , with the scaling factor  $a$  differing between low ( $<1$  Hz) and high ( $>1$  Hz) frequency bands. When shown on logarithmic axes, such power-law scaling translates into a straight line with slope  $a$ , as illustrated in Figure 1A.

It is important to note the distinction between the spectral  $1/f^a$  shape and rhythmic oscillatory activity. Oscillatory activities with well-defined frequencies (e.g., theta, alpha, or gamma oscillations) are prevalent in neural networks and result

in distinct peaks above the  $1/f^a$  background (Buzsaki, 2006) (cf. Figure 1A). Typically, such oscillations result from processes with well-defined intrinsic timescales and can be associated with defined networks such as thalamocortical or hippocampal loops. In contrast to this, activity characterized by a (straight)  $1/f^a$  spectrum is considered "arrhythmic," as it does not reflect processes with identifiable timescales. Systems that generate perfect power-law spectra are also known as "scale-free," since the underlying process or network possesses no distinguished scale (Bak et al., 1987; Jensen, 1998). Importantly, while oscillations have attracted wide interest and are matter of various speculations with regard to their meaning and function, the arrhythmic component of electric brain activity is often considered self-evident or uninteresting and hence ignored.

The stunning finding of He et al. is that even such supposedly arrhythmic brain activity has a complex temporal structure in the form of crossfrequency phase-amplitude coupling. Crossfrequency implies that the coupling involves two distinct frequency bands, and phase-amplitude implies that the amplitude of one band is dependent on the phase of the other. In particular, He et al. extracted band-limited components from their wide-band signals and found that the amplitude of the faster component depends on the phase of the slower one, as illustrated in Figure 1B. For their analysis they considered a range of frequency pairs and used statistical bootstrapping methods to validate the significance of phase dependency. Overall, they found

that more than 70% of the electrodes contained frequency pairs with significant frequency coupling. Importantly, and to prove the importance of this phenomenon, they demonstrated the existence of crossfrequency coupling not only in resting state activity, but also during task performance and slow-wave sleep.

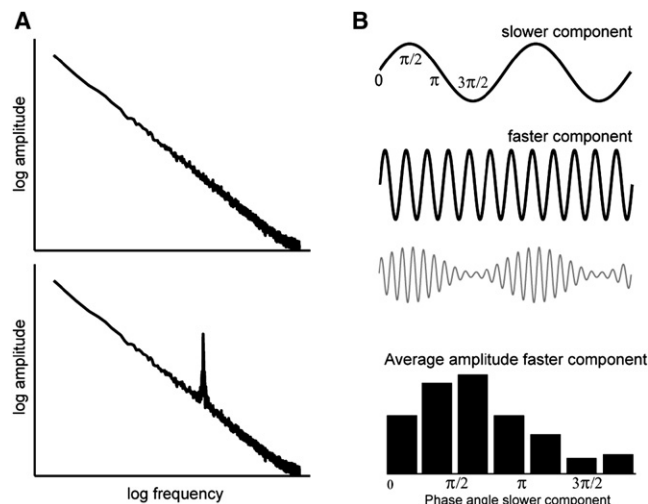
Previously, such crossfrequency coupling had only been noted in the context of oscillatory activity. In auditory cortex, for example, the amplitude of gamma band ( $>30$  Hz) oscillations or multiunit spiking activity ( $>300$  Hz) is modulated by the phase of slow theta (4–8 Hz) or delta (1–4 Hz) rhythms (Lakatos et al., 2005). Yet, in contrast to He et al.'s study of arrhythmic activity, theta or delta oscillations have a direct biophysical interpretation: troughs and peaks of the periodic signal indicate periods of increased and decreased local network excitability (Buzsaki, 2006). The scaling of multiunit activity with the phase of slow rhythms hence reflects the dependency of neural responses on the local network state (Lakatos et al., 2005). Consistent with this interpretation, a recent study reported that the behavioral performance of subjects in a visual task covaries with the phase of slow occipital EEG rhythms, hence the presumed excitability of visual cortex (Busch et al., 2009). With arrhythmic activity, on the other hand, there is no clear biophysical interpretation of narrow-band components. That the new study explicitly reports crossfrequency coupling for electrodes without distinct spectral peaks (i.e., prominent oscillations) thus suggests that crossfrequency coupling is more widespread than previously thought and

that it is relevant for phenomena beyond brain rhythms. Still, as the authors themselves note, by “absence of evidence argument” their results can only suggest but not prove cross-frequency coupling in the absence of oscillations.

Having shown the existence of crossfrequency coupling in brain activity, the authors then asked whether similar frequency coupling also occurs in other complex processes that generate power-law frequency spectra. Power-law spectra characterize processes with long-range correlations and have been reported for a wide range of biological, physical, and economic processes, including avalanches, earthquakes, and economic indices (Kello et al., 2010; Jensen, 1998; Lima-Mendez and van Helden, 2009). In their

study, He et al. applied their analysis procedures to data recorded by seismometers (earthquake detectors) and the Dow-Jones Industrial Average index. To their surprise, the authors found prominent and widespread crossfrequency coupling in both datasets, much as they had observed in ECoG's. In addition, they also analyzed well-defined and simulated toy processes. While these were able to capture general properties of a  $1/f^2$  spectrum, most of them did not reveal crossfrequency coupling. Surprisingly, however, the authors found that pseudorandom processes generated using certain (imperfect) random number generators did show crossfrequency coupling, perhaps a consequence of the deterministic means by which the numbers are generated.

The combined evidence from the different datasets lends itself to the speculation that this frequency coupling is dependent on a combination of long-range correlations and higher-order statistical regularities in the underlying processes. However, caution is required when making such interpretations. First, while long-range correlations or scale-free properties have been mentioned in



**Figure 1.**

(A) The upper panel displays a hypothetical power spectrum with  $1/f^2$  shape without distinct oscillations. The lower panel displays the same power spectrum with an added oscillation, visible as a clear peak above the straight line. (B) Idealized example of phase-amplitude coupling. The upper two panels illustrate two (oscillatory) signals of different frequencies. The gray line displays the faster signal amplitude modulated by the slower signal, in such a way that the amplitude of the faster signal peaks at the phase of  $\pi/2$  of the slower signal. The bottom panel displays the same in the form of a hypothetical phase-separated amplitude histogram, as used in the discussed study.

conjunction with biophysical processes, it is important to note that simply being able to describe data with a  $1/f^a$  curve does not imply that the underlying processes indeed concords with these theoretical concepts (Fiete et al., 2010; Kello et al., 2010; Jensen, 1998; Lima-Mendez and van Helden, 2009). For example the linear superposition of a large number of randomly occurring and exponentially decaying postsynaptic currents can produce processes with long-range interactions and can account for the spectral shape of cortical field potentials (Bédard and Destexhe, 2009; De Los Rios and Zhang, 1999). Thus, whether long-range correlations are indeed necessary for frequency coupling remains to be tested.

In addition, the kind of higher-order statistical regularities that could serve as a source for crossfrequency coupling remains to be elucidated. In this regard it is interesting to note that the pattern of frequency coupling was stable across waking, slow-wave sleep, and a cued button-press task, suggesting regularities common to all these conditions. This robustness stands in contrast to changes observed in the frequency spectra, where changes in spectral slope and the emer-

gence of additional oscillatory peaks were prominent across conditions. It could be taken to suggest that the observed coupling reflects structural (and hence stable) rather than functional (and hence dynamic) properties of the underlying networks.

On the technical side, it remains to be seen how sensitive the results of He et al. are with respect to parameters used for the extraction of band-limited signal components. When investigating distinct oscillations (e.g., theta or alpha oscillations) the choice of frequency ranges can be straightforward. However, when investigating arrhythmic signals, a priori choices must be made about the frequency bands to be used, and the choice of spectral filtering method or parameters such as band separation

or band width determine the tradeoff between temporal and frequency resolution. That the authors provide the computer code for their analysis will definitely help to systematically explore such questions.

What can these findings tell us about the generators of brain activity? The ECoG represents a measure related to local field potentials. The cortical sources and biophysical properties of field potentials have been a matter of considerable interest and several recent studies investigate their biophysical sources, their spatial specificity, and the coupling between field potentials and spiking activity (see e.g., Bédard and Destexhe, 2009; Logothetis et al., 2007; Pettersen and Einevoll, 2008). The overall shape of field potential spectra is a result of the superposition of many processes that cover a range of timescales (spikes, postsynaptic potentials, afterpotentials, etc.), and the macroscopic trace of each individual process in turn reflects the biophysical constraints on the generating currents. Coupling of faster and slower components of the aggregate field potential could thus reveal dependencies of different components of the compound signal. As such,

frequency coupling could be used to constrain models of field potential generation. In turn, such models could also be used to elucidate whether there are indeed processes of distinct frequencies that are coupled in the described manner. Such combined model and data-driven investigations will be necessary to ultimately decide whether the reported crossfrequency coupling actually constitutes a phenomenon with biological sources and relevance.

On the whole, these new results draw attention to the arrhythmic components of neural mass activity and highlight that also apparently unspectacular and often ignored signals can reveal surprisingly complex structure.

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# Losing Phase

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**In this issue of *Neuron*, Remme and colleagues examine the biophysics of synchronization between oscillating dendrites and soma. Their findings suggest that oscillators will quickly phase-lock when weakly coupled. These findings are at odds with assumptions of an influential model of grid cell response generation and have implications for grid cell response mechanisms.**

As our moon orbits the Earth, it rotates. Yet on Earth we see only one face of the moon. This happens because the moon happens to rotate by exactly the same amount that it revolves. The matching of angular speeds for rotation and revolution is no coincidence. It is the inexorable result of the periodic movements of the earth and moon combined with the weak gravitational tidal forces coupling them. In the language of the theory of coupled oscillators, the moon's rotation and revolution have converged to the stable phase-locked solution.

In this issue of *Neuron*, Remme et al. (2010) use the theory of weakly coupled oscillators to provide a compelling analysis of the biophysical viability of an influential model of grid cell response generation. Rats and mice (Fyhn et al., 2008 and

references therein) have grid cells, and there is good evidence for their presence in humans (Doeller et al., 2010). A single grid cell responds as a function of animal location in two-dimensional (2D) space, with a firing peak at every vertex of a (virtual) regular triangular lattice that covers the plane. The spatial period of the grid cell response is independent of animal speed.

Models of grid cell activity fall into two main classes, both predicated on the hypothesis that position-coded grid cell responses are obtained using animal-velocity cues. Aside from this shared hypothesis, the model classes are disparate in their assumptions and predictions, with each class explaining largely complementary subsets of grid cell properties. One model class assumes that strong

network-level recurrent connectivity unleashes a spontaneous patterning of the neural population response (Fuhs and Touretzky, 2006; McNaughton et al., 2006; Burak and Fiete, 2009, and references therein). These population responses translate into spatially periodic responses of single neurons. The other model class assumes that interfering temporal oscillations set up a beat wave that can be mapped onto space to produce spatially periodic grid responses (Burgess et al., 2007; Hasselmo, 2008).

Remme and colleagues analyze an exemplar of the temporal interference (TI) models, based on voltage oscillations within a single neuron (Burgess et al., 2007). The model may be summarized as follows: if the soma oscillates at a fixed temporal frequency, and a dendrite